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Development of a Standard Protocol for the Harmonic Analysis of Radial Pulse Wave and Assessing Its Reliability in Healthy Humans

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ABSTRACT This study was aimed to establish a standard protocol and to quantitatively assess the reliability of harmonic analysis of the radial pulse wave measured by a harmonic wave analyzer (TD01C system). Both intraobserver and interobserver assessments were conducted to investigate whether the values of harmonics are stable in successive measurements. An intraclass correlation coefficient (ICC) and a Bland–Altman plot were used for this purpose. For the reliability assessments of the intraobserver and the interobserver, 22 subjects (mean age 45 ± 14 years; 14 males and 8 females) were enrolled. The first eleven harmonics of the radial pulse wave presented excellent repeatability (ICCs > 0.9 and $p < 0.001$) for the intraobserver assessment and high reproducibility (ICCs range from 0.83 to 0.96 and $p < 0.001$) for the interobserver assessment. The Bland–Altman plot indicated that more than 90% of harmonic values fell within two standard deviations of the mean difference. Thus, we concluded that the harmonic analysis of the radial pulse wave using the TD01C system is a feasible and reliable method to assess a hemodynamic characteristic in clinical trial.

INDEX TERMS Harmonic analysis, radial pulse wave, blood pressure, reliability.

I. INTRODUCTION

Pulse wave analysis (PWA), extracting characteristic features of pressure pulse either from time domain or from frequency domain, has been extensively used in monitoring cardiovascular disease [1], [2]. Traditionally, the assessment of circulatory function relies on the brachial blood pressure measurement, where systolic pressure [3], diastolic pressure [4], [5], and pulse pressure [6] has been proved correlated with cardiovascular event. In recent years, the clinical interest has increasingly focused on arterial stiffness. Therefore, the markers of arterial stiffness such as pulse wave velocity (PWV) and augmentation index (AIx) were studied in aging [7], [8], hypertension [9], [10], coronary artery disease [11], [12], and renal disease [13], [14].

However, those variables mentioned above, extracting time-domain features from pulse, are only a partial description of the pressure wave [2]. To obtain a complete quantitative expression of the pressure wave, harmonic analysis (HA) is one of the most satisfactory approaches [2]. HA is a basic frequency analysis in periodic signal, using Fourier series calculation to decompose the arterial pulse wave into harmonic components, also abbreviated harmonics [15].

One branch of HA is generalized transfer function, where scaling relationships between two measurement sites were calculated in terms of amplitude and phase as a function of harmonics of pressure wave. O'rourke et al. applied the generalized transfer function to reconstruct the waveform of central aortic pressure wave from either the brachial or radial blood pressure wave [16].

Wang et al. used HA in another perspective, where those harmonic components were deemed as a set of basic characteristics of whole arterial system [17]. Thus, the variation of harmonics reveals variation of status of the arterial system, which has been proved a useful method in cardiovascular researches [18]. According to the observation of the previous researches, Lin Wang et al. developed a PS wave model to simulate the low damped oscillation of arterial pressure

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wave [19]–[24] and to elaborate the meaning of the harmonic components in cardiovascular physiology [25], [26].

Based on the PS wave model, Jan et al. proposed that HA can reveal the function of the organs [27]. Wang et al. found that harmonic components are correlated with liver function [28]–[30], with acute uncomplicated myocardial infection [31], and with hypertension [32], [33]. Furthermore, harmonic components are also used in examining the effects of Chinese herb [34]–[39] and acupuncture [40]–[42].

In spite of the various clinical application of HA were proposed, the reliability of HA in clinical study has not confirmed. The accuracy of harmonics can be affected by several measurement factors such as effective size of sensor, control of tensile force, and the net force on the tissue surface. Those measurement factors might cause potential errors and threaten the credibility of HA.

Therefore, validating the reliability of the harmonic components of the arterial pulse wave are necessary to ensure valid interpretation of HA, to determine the correlation between HA and cardiovascular disease, and to quantify the effects of Chinese herb and of mechanical therapies. In other word, a reliable instrument and a standard protocol should be applied to provide assurance that each time an individual is observed, the harmonic changes are due to the different arterial condition rather than inconsistent measurement capabilities of the instrument.

To achieve the goals mentioned above, the objective of the study was to investigate that, in successive measurements, whether the harmonic components are repeatable by same observer and are reproducible by different observers. Both of the measurements will calculate the intra-class correlation coefficients (ICC) and use Bland-Altman plot to examine the degree of the agreement.

II. MATERIAL AND METHODS

A. HARMONIC WAVE ANALYZER TD01C

TD01C (MII-ANN Technology, Taiwan) is a noninvasive system that detects the blood pressure pulse of the radial artery and analyzed the pressure pulse in frequency domain. TD01C has an effective and continuous sensing surface (>2.0 cm^2). TD01C has architectures of dynamic range adjustment and of automatic pulse-sensing such that it can analyze pressure data within minutes and reach resolution of the 11 harmonic waves. TD01C should operate within working condition: 0∼2.5 PSI (peak to peak pressure), 23°C-35°C, and 15% to 85% Relative humidity. The instrument reliability of TD01C had been validated before the measurements were performed [43].

B. STUDY PROTOCOL

Each assessment was performed after 10-minute rest in a quiet room at controlled temperatures of ranging from 23-25 °C. Drinking alcohol, tea, and coffee was not allowed for 4 hour before assessment. All the observers needed to read the instruction manual of harmonic wave analyzer TD01C. The standard process listed below for each assessment:

1. Require the subject to sit up straight.
2. Measure the wrist circumference of the subject.
3. Find the skin surface over the radial artery with maximum pulse pressure, and mark it.
4. Attach the TD01C sensor on the skin surface mentioned above.
5. Strap the wristband with appropriate length corresponding to the wrist circumference.
6. Check that signal exceeds 1/3 Full scale on the screen.
7. Adjust the angle between the surface of the sensor and the skin, so that amplitude of the signal is maximized.
8. Start the formal assessment.

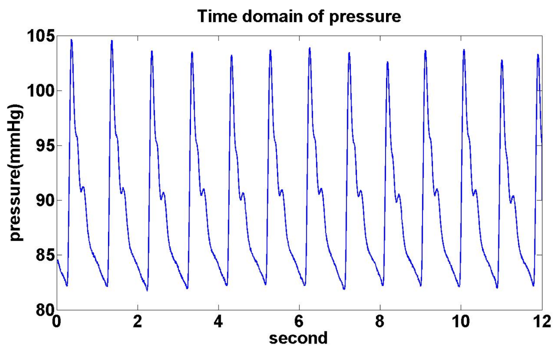

FIGURE 1. A typical 12-second radial pulse wave recorded by harmonic wave analyzer TD01C at sampling rate of 400 Hz.

C. DATA ACQUISITION AND HARMONIC ANALYSIS

In each measurement, the 12-second data were recorded by harmonic wave analyzer TD01C at sampling rate of 400 Hz (Figure 1). All pulses were separated sequentially by the minimum points from pulse peak to pulse peak. Each pulse was transformed into Fourier series coefficients ($A_{n,i}$) and then normalized by the mean value of the pulse ($A_{0,i}$), where i indicated the ith pulse in twelve-second data and n indicated the nth harmonic components of the pulse. The representative amplitude of harmonic component (C_n) within one measurement was defined by following equation, where N is the total number of pulses within the 12-second measurement.

$$C_n = \frac{1}{N}\sum_i \frac{A_{n,i}}{A_{0,i}}$$

In this study, we focused on the first eleven harmonic components ($n = 1\sim11$). For each harmonic component, the within-measurement standard deviation (σ_{cn}) and coefficient of variation (WCV_{cn}) were calculated by following equation

$$\sigma_{cn} = \sqrt{\frac{\sum_{i=1}^{N}\left(\frac{A_{n,i}}{A_{0,i}} - C_n\right)^2}{N-1}}$$

$$WCV_{cn} = \frac{\sigma_{cn}}{C_n}$$

$C_1\sim C_{11}$ were representative parameters that described the characteristic of sequential pulses, and $WCV_{c1}\sim WCV_{c11}$

represented the degree of variation among sequential pulses within the measurement.

D. ASSESSMENT OF INTRA-OBSERVER REPEATABILITY

Twenty two subjects (aged 27-70; mean age 45 ± 14 years; 14 males and 8 females) were enrolled for the assessment of intra-observer repeatability from staffs and students of National Taiwan University. Observer 1 measured the harmonic components (C_ns) of radial pulse wave twice for each participant with 5 minutes between measurements.

E. ASSESSMENT OF INTER-OBSERVER REPRODUCIBILITY

Twenty two subjects (aged 27-70; mean age 45 ± 14 years; 14 males and 8 females) were enrolled for the assessment of intra-observer repeatability from staffs and students of National Taiwan University. For each subject, the harmonic components (C_ns) of radial pulse wave were measured by Observer 1 and Observer 2 in random order. A minimum of 5 minutes was allowed between measurements, and wristband was retied at the second measurements.

Volunteer recruitment was after receiving approval from the institutional review board of the RenAi Branch of Taipei City Hospital (IRB number: TCHIRB1010710).

F. STATISTICS

1) BLAND-ALTMAN ANALYSIS

The intra-observer and inter-observer reliability assessment was evaluated using the Bland-Altman analysis [44], which is widely accepted and used for reliability validation. For each harmonic component, the difference between successive measurements was plotted against their mean value. Then the mean ($\bar{d}$) and the standard deviation (SD) of differences for all participants were calculated. Limits of agreement ($\bar{d} \pm 2$SD) were marked by dash lines (Figure 2).

2) INTRACLASS CORRELATION COEFFICIENT

For the intra-observer and inter-observer reliability assessment, two-way random *single-measure* intraclass correlation coefficients, ICC $(2, 1) = \rho$, were calculated with Matlab 2008, USA. According to the suggestion of Fleiss [45], the value $\rho > 0.75$ was deemed as excellent reliability. Furthermore, Portney and Watkins [46] recommend that $\rho > 0.9$ is appropriate for clinical application to ensure valid interpretation (Table 1).

III. RESULT

A. RESULT OF INTRA-OBSERVER ASSESSMENT

Bland-Altman plots were constructed for all harmonics of intra-observer assessment. Three examples (C9, C10, C11) of the plot for pairs of measurements assessed by observer1 are shown in Figure 2. For all harmonics the mean differences were near to the zero. Intraclass correlation coefficient for repeatability, ICC (2, 1), were summarized in Table 1, which presents that all the ICCs exceeded 0.9 for all harmonics in the intra-observer case.

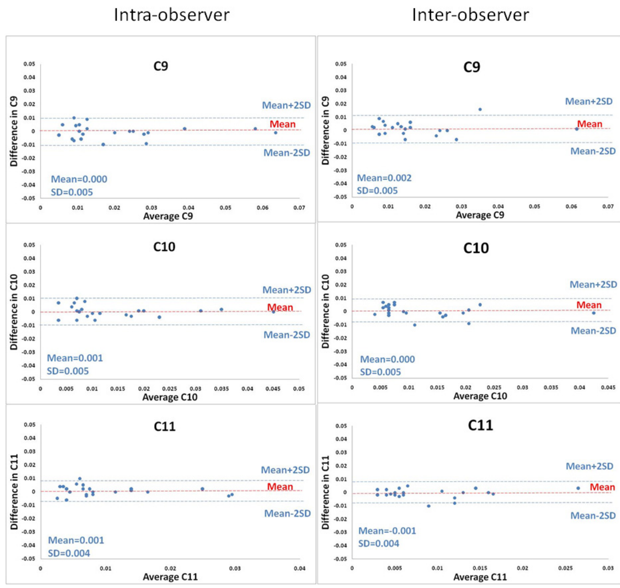

FIGURE 2. The Bland-Altman plot of the harmonic components (C9, C10, C11) of the arterial pulse wave. The left part is the intra-observer repeatability assessment (N = 22) and the right part is the inter-observer reproducibility assessment (N = 22).

B. RESULT OF INTER-OBSERVER ASSESSMENT

Bland-Altman plots were used to visualize all harmonics of inter-observer assessment. Figure 2 shows three plots (C9, C10, C11) for successive measurements assessed by observer1 and observer 2 in a random order. For all harmonics the mean differences were all near to zero. Intraclass correlation coefficients for reproducibility, ICC (2, 1), were summarized in Table 1. ICCs of some harmonic components (C5, C6, C10, C11) reach 0.88, 0.89, 0.88, 0.83 respectively, and ICCs were above 0.9 for all the other harmonics case.

IV. DISCUSSION

From the result of intra-observer assessment (Table 1), the ICC (2, 1) of the first five harmonics were all greater than 0.9 with p-value less than 0.001, which significantly confirmed that the variation of the harmonics in repeatability study were mostly caused by population variation rather than variation between two successive measurement. The reliability of repeated measurement reached the suggested criteria of the clinical application level [46].

The result of inter-observer assessment (Table 1) showed that the ICC (2, 1) of the first five harmonics were all greater than 0.83 with p-value less than 0.001, which significantly confirmed that the variation of the harmonics in reproducibility study were mostly caused by population variation rather than variation caused by two observer. The reliability of reproducible measurement was good enough for Fleiss recommended level [45] but still had room for improvement.

In other studies, repeatability of AIx were examined, where intra-observer ICC ranged from 0.75 to 0.96 [47]–[49] and inter-observer ICC ranged from 0.92 to 0.93 [47];

TABLE 1. The intra-observer and the inter-observer (N = 24) reliability assessment of the harmonic components of the arterial pulse wave using intraclass correlation coefficient. For each harmonic component, SD is the standard deviation of differences (N = 24) between two of successive measurements.

	Intra-observer assessment			Inter-observer assessment		
	SD	ICC	P value	SD	ICC	P value
C_1	0.027	0.97	3.1E-14	0.040	0.94	3.9E-11
C_2	0.022	0.96	2.6E-13	0.053	0.93	6.9E-11
C_3	0.032	0.95	1.9E-12	0.039	0.96	1.6E-13
C_4	0.014	0.97	1.2E-14	0.021	0.94	6.0E-12
C_5	0.010	0.96	6.1E-13	0.022	0.88	2.3E-08
C_6	0.016	0.98	1.1E-16	0.019	0.89	6.3E-09
C_7	0.013	0.95	5.6E-12	0.009	0.94	2.4E-11
C_8	0.007	0.91	6.1E-10	0.006	0.92	3.4E-10
C_9	0.005	0.97	6.0E-14	0.005	0.92	2.7E-10
C_{10}	0.005	0.95	6.1E-12	0.005	0.88	1.7E-08
C_{11}	0.004	0.97	1.0E-14	0.004	0.83	4.2E-07

Intra-observer ICC of PWV ranged from 0.75 to 0.92 [50]–[52] and inter-observer ICC of PWV was 0.88 [53]; The intra-observer ICC of central systolic blood pressure reconstruct from transfer function was 0.74 in resting state [48]. Comparing to other index of PWA, the harmonic components are competitive and reliable.

From aspect of signal analysis, the radial pulse wave is an almost periodic signal, which conserves the most energy in its fundamental frequency and harmonics. Furthermore, the harmonic components are orthogonal basis which completely represent the whole pulse signal. Therefore, to examine stability of the radial pulse wave, assessing reliability of its harmonic components is satisfactory and necessary. We suggest that all measurements of radial pulse wave should assess the reliability of harmonics before transforming the pulse into specific parameters.

HA has been used in cardiovascular study for many clinical applications. Jan et al. proposed that HA can reveal the function of the organs in pressure pulse spectrum [27], and Hsu et al. found that harmonic components could be a real time biomarker for liver function [28]. Since the TD01C is a noninvasive system that detects the radial artery pulse and has good reliability of HA, it reveals the good potential to assess the function of the organ in real time. Nevertheless, HA is suitable for the effects of taking Chinese medicine by percentage change of harmonics of radial artery pulse [54].

The effects of acupuncture at Tai-Tsih (K-3) [40], at Tsu San Li (St-36) [41], and at Hsien-Ku (St-43) [42] were studied using HA in health human. Furthermore, Hsiu proved that increments of fifth and sixth harmonics were related to increment of brain perfusion during acupuncture intervention in stroke patient [55]. Hence, harmonic amplitude increment has potential to be a real-time and noninvasive biomarker during or after intervention.

To estimate the effect of acupuncture or Chinese Herb, the differences of harmonic components between pre- and post-intervention should take intra-observer errors into consideration. According to the intra-observer result, we suggested that the change of C1∼C11 should exceed SDs 0.027∼0.004 respectively (Table 1) to interpret the change of specific harmonic component; roughly, to verify the change before and after intervention, C1∼C2 should exceed about 5% change; C3∼C5 should exceed about 10% change; C6∼C8 should exceed about 20% change; C9∼C11 should exceed about 40% change. If a smaller minimal detectable difference of harmonic was needed, the sample size should be re-estimated. Therefore, in order to overcome the intra-observer error and to validate the effective change of harmonics between measurements, this report could be used as a guideline and reference to estimate the number of subjects needed.

In addition, if a meta-analysis such as comparing acupuncture effect at K-3, at St-36, and at St-43 was performed, the inter-observer error should take into account. Thus, more minimal detectable difference is needed to overcome the effect inter-observer error. The methodology and criteria could be a guideline to select the results appropriate for further clinical interpretation. The criteria could also be a reference to estimate the appropriate sample size.

This report focused on harmonics amplitude between intra-observer and inter-observer measurements. The harmonic amplitudes were used as representative characteristics to estimate reliability of HA in arterial pulse wave. There are still two parameters need to be further investigated in the future. One is the coefficient of variation of harmonic amplitude among pulses within one measurement (WCV_{cn}). Since the WCV_{cn}s were less than 3% using TD01C in the phantom study [43], the WCV_{cn}s beyond 3% revealed that the variation were partially introduced by the arterial system of the subject. The previous reports had shown that this within-measurement variation of the harmonics reflected the stage of severity in dying patients [56], [57]. Therefore, the WCV_{cn}s could also been meaningful biomarkers that reveals function or status of the arterial system and need more studies to prove the conjecture. Second parameter is the phase of harmonic components, which still need more exploratory studies.

In summary, the report confirmed that HA of radial pulse wave using TD01C system was a feasible and reliable method to assess hemodynamic characteristic in clinical study. Harmonic components has been proved correlated with some cardiovascular function and disease [18]. Since TD01C measures radial pulse wave noninvasively and takes only

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minutes to practice the standard protocol, HA can be used in monitoring cardiovascular disease in real time. The noninvasive nature of TD01C allows repeated measurements over time to study the effectiveness of various interventions that may affect cardiovascular system. This report is a beginning and a bridge to discover what the pressure wave tells us and to utilize the information in clinical practice.

V. CONCLUSION

The primary findings of this research demonstrate that, following the standard protocol, TD01C system is a reliable instrument for HA of radial pulse wave. TD01C system has not only the good repeatability of intra-observer measurement but also high reproducibility of inter-observer measurement.

The good reliability of harmonic analysis, combining with previous clinical finding in reference, showed the great niche and potential for further usage in cardiovascular diagnosis and intervention. The research built up the protocol and criteria for intra-observer and for inter-observer measurements to validate the effective change of harmonic component before and after intervention. This report could help bridging laboratory studies to clinical applications.

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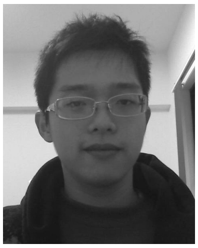

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